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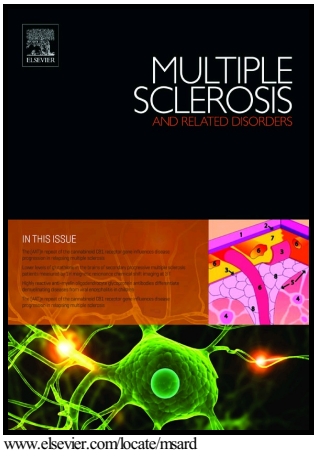

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Pulmonary Sarcoidosis in a patient with Multiple Sclerosis on Daclizumab monotherapy

Authors: Elijah Edward Rhone[a]; Peter Siu Pan Cho[b]; Surinder S. Birring[bc]; James Galloway[c]; Eli Silber[a]

[a]Department of Neurology, King's College Hospital, Denmark Hill, London, SE5 9RS, UK
[b]Division of Asthma, Allergy and Lung Biology, King's College London, Weston Education Centre, Denmark Hill, London SE5 9RJ, UK
[c]Department of Respiratory Medicine, King's College Hospital, Denmark Hill, London, SE5 9RS, UK
[d]Department of Rheumatology, King's College London King's College London, Weston Education Centre, Denmark Hill, London SE5 9RJ, UK
[e]Department of Rheumatology, King's College Hospital, Denmark Hill, London SE5 9RS, UK

Corresponding author:
Dr Elijah Rhone
Clinical Research Fellow in Neurology
King's College Hospital,
Denmark Hill,
London, England
SE5 9RS
Phone: (+44) 2032991905
Fax: (+44) 2032993587
Email: erhone@nhs.net

Co-author contact details
Peter Cho: p.cho@nhs.net
Surinder Birring: surinder.birring@nhs.net
James Galloway: james.galloway@kcl.ac.uk
Eli Silber: eli.silber@nhs.net

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ABSTRACT

As new immunomodulatory therapies continue to be licensed for use in Multiple Sclerosis, it is important to remain vigilant for new, unexpected associations relating to these medications. We highlight this by reporting on a case of a 45-year-old man who developed systemic, non-specific symptoms following long term use of daclizumab and was subsequently diagnosed with sarcoidosis. We go on to briefly discuss the action of daclizumab, in particular the effect it has on $CD56^{bright}$ natural killer cells, a cell type that has been investigated in relation to sarcoidosis.

CASE DETAILS

A 45-year old Caucasian male presented with a 2-month history of fevers, night sweats and non-productive cough. He had been on a series of consecutive trials of daclizumab for Relapsing Remitting Multiple Sclerosis (RRMS), totalling 79 months (12-months placebo-controlled, 12-months dose-blinded, 55-months open-label of 150mg monthly subcutaneously). He had experienced three relapses in the three years prior to commencing the trials but remained relapse-free during them. He had no significant co-morbidity. Physical examination revealed new bilateral inguinal lymphadenopathy. Neurological examination demonstrated longstanding altered left-sided facial sensation, mild instability on Romberg testing; Expanded Disability Status Scale (EDSS) score was stable at 2.0. Investigations revealed elevated ESR (35mm/hr), ACE (62 IU/L), IgG (27.65 g/L), IgM (5.51 g/L) and total protein (91 g/L) but were otherwise unremarkable (lymphocyte count 1.72 10^9 g/L, corrected-calcium 2.35 mmol/L). Daclizumab was suspended pending further investigation. CT-PET confirmed high avidity lymphadenopathy in the mediastinum and abdominal chains, but no visceral uptake (figure a). Lymph node aspirate obtained via endobronchial ultrasound demonstrated non-necrotising granulomatous inflammation (figure b).

Brain MRI before/after gadolinium was stable with no new or enhancing lesions and no meningeal enhancement. Two months following daclizumab cessation, spirometry demonstrated moderate obstruction; FEV1 2.13 (62.3% predicted), FVC 3.62 (83.7% predicted), FEV1/FVC ratio 58.8%. At this point, all symptoms except the non-productive cough had resolved. No alternative aetiology was identified and a clinical diagnosis of sarcoidosis was made. Inhaled corticosteroids were commenced followed by a short trial of oral corticosteroids, both of which had no effect on the cough.

CT-PET 6-months following daclizumab cessation demonstrated reduction in lymph node uptake. Repeat spirometry 10-weeks following discontinuation of corticosteroids was normal; FEV1 3.01 (88% predicted), FVC 3.74 (86.5% predicted), FEV1/FVC ratio 80.5%. Considering subjective and objective evidence of improvement following daclizumab cessation, it was reasoned that daclizumab was the probable cause and it was therefore permanently discontinued.

DISCUSSION

Sarcoidosis is a multi-system granulomatous disorder that most commonly affects the pulmonary and lymphatic systems. In most patients, granulomas resolve spontaneously or following appropriate therapy (e.g. corticosteroids with or without steroid sparing agents such as methotrexate). A minority of patients develop chronic progressive disease, characterised by persisting granulomas, which may undergo fibrosis, causing irreversible organ damage. Sarcoid granulomas are characterised by monocytes, macrophages and activated T cells, with interleukin-2 (IL-2) a driver cytokine of this Th1-type cellular response.[1]

Daclizumab is a monoclonal antibody approved for treatment of RRMS. Trials have demonstrated its efficacy in reducing relapses, disability progression and development of new MRI lesions[2]. Daclizumab binds to the alpha chain (CD25) on high-affinity IL-2 receptors, inhibiting the association of IL-2 with the receptor. The IL-2 pathway is involved in activation, proliferation and differentiation of T cells and daclizumab is hypothesised to suppress IL-2-mediated T-cell expansion and activation[2]. The current understanding of sarcoid immunopathology makes its occurrence paradoxical in the setting of Daclizumab therapy. One speculative hypothesis lies in the effect of daclizumab on natural killer cells. $CD56^{bright}$ cells are a subset of natural killer (NK) cells, observed in small numbers in

peripheral blood but as a much greater proportion within lymph nodes[3]. These cells are immunoregulatory and have the capacity to produce a range of inflammatory cytokines (e.g. TNF-α, IFN-γ) when activated[3]. CD56^{bright} NK cell populations expand significantly during daclizumab therapy. The proposed mechanism is that blockade of high-affinity IL-2 receptors leads to reduced IL-2 consumption as well as increased IL-2 production due to lack of negative feedback resulting in increased local availability of IL-2. CD56^{bright} NK cells express an intermediate-affinity IL-2 receptor. Daclizumab does not interact with this receptor allowing IL-2 to bind freely, resulting in cell proliferation[2].

Interestingly, higher numbers of CD56^{bright} cells have been observed in broncho-alveolar lavage fluid of individuals with sarcoidosis compared to controls[4] and higher proportions of NK cells in this fluid have been found to correlate with a poor prognosis[5]. However, an expansion of CD56^{bright} cells can be seen in a range of diseases and it is unclear if they are a driver of disease or a consequence of the pathological process[3].

In a review of daclizumab, the Center for Drug Evaluation and Research (a division of the U.S. Food and Drug Administration), with access to raw trial data, identified nine cases of sarcoidosis amongst various RRMS trial cohorts, with another four potential cases. Based on these nine confirmed cases, the incidence of sarcoidosis was estimated to be approximately 1.32/1,000 patient years compared to a reported rate in the general population of 1.0-35.5 per 100,000/year[6]. One case of sarcoidosis has also been reported in a patient treated off study with another form of daclizumab in adult T-cell leukaemia/lymphoma[7].

The development of sarcoidosis has also been observed following the use of other disease modifying therapies. Several cases have been reported following the use of interferon-β,

including specifically in patients being treated for multiple sclerosis[8]. There have also been reports of cases following the use of alemtuzumab[9] and natalizumab[10] in the treatment of other diseases; although to our knowledge, there are no reports in the literature of the development of sarcoidosis in patients treated with these medications for multiple sclerosis. This case emphasises the need to be vigilant for unexpected associations when using novel immunomodulatory therapies.

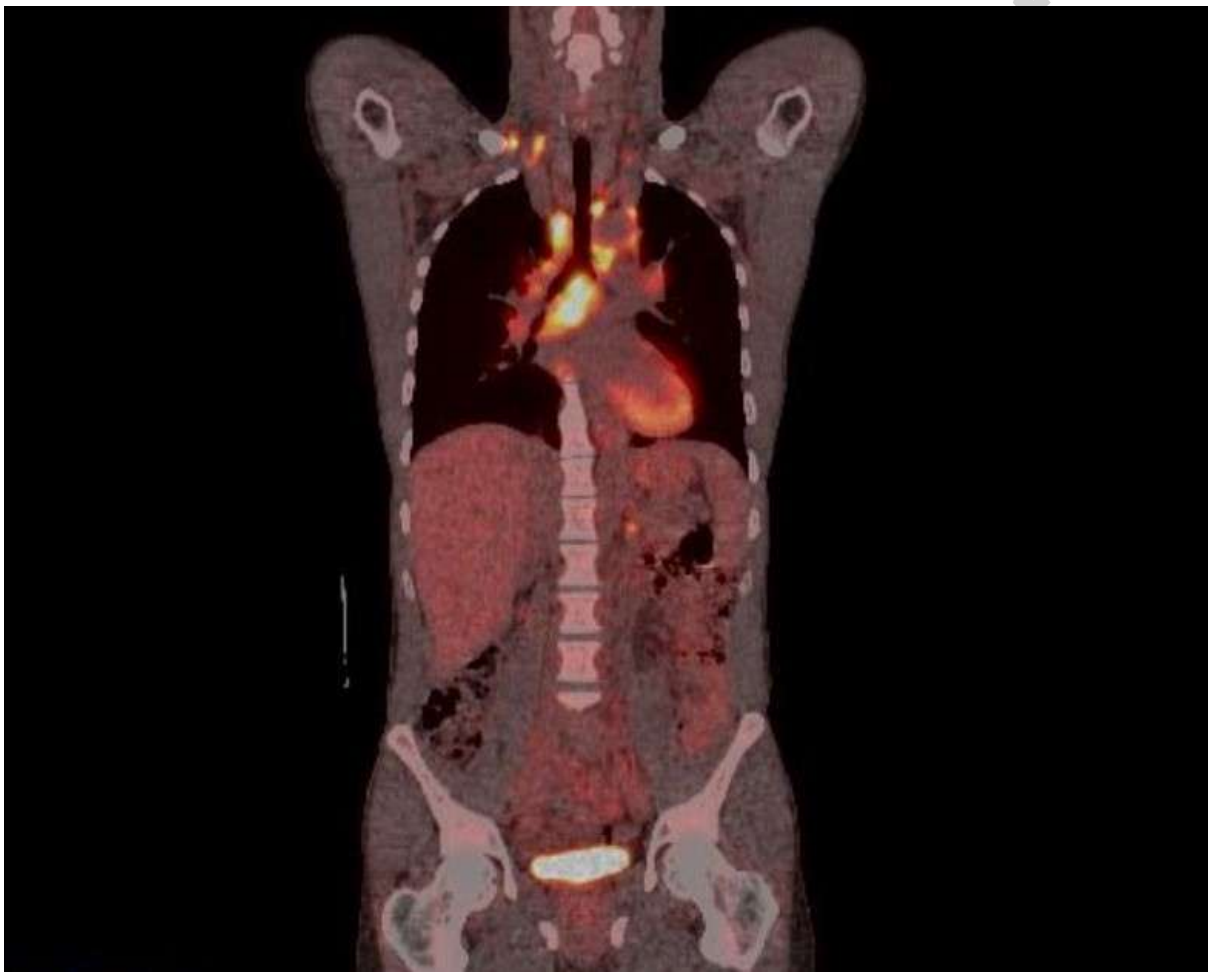

Figure a - PET- CT demonstrating metabolically active mediastinal lymphadenopathy

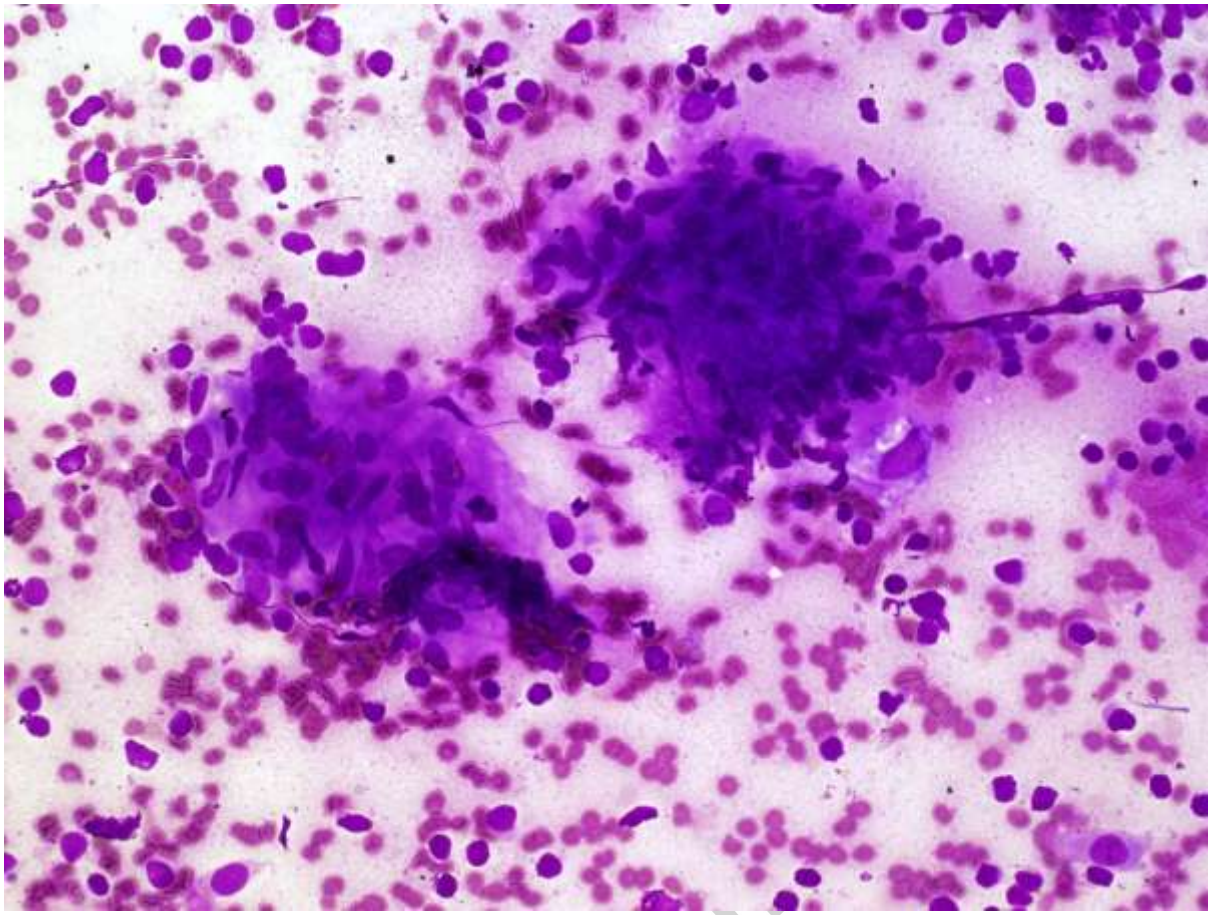

Figure b - Cytology photomicrograph demonstrating granulomas following EBUS sampling

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We would like to thank Dr Emma Mclean, consultant histopathologist at Guy's and St Thomas' Hospital for providing the cytology image.

Consent

The patient provided written consent for the details of this case to be published in an anonymised fashion.

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HIGHLIGHTS

- Daclizumab is a relatively new disease modifying therapy for treatment of RRMS
- A case of a 45 year old man developing sarcoidosis following daclizumab therapy
- Current understanding of sarcoid immunopathology makes its occurrence paradoxical in the setting of Daclizumab therapy
- Important to be vigilant for unexpected associations when using novel immunomodulatory therapies